



AT-11614/4#
CASE LA 24A #19
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Ronald S. Hermenau
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Ronald S. Hermenau
Signature

March 14, 2002
Date

APR 03 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Art Unit: 1614

ROBL ET AL.

Examiner: Moezie, F.

APPLICATION NO: 09/391,053

FILED: SEPTEMBER 7, 1999

FOR: METHOD FOR TREATING DIABETES EMPLOYING AN AP2
INHIBITOR AND COMBINATION

Assistant Commissioner for Patents
Washington, D.C. 20231

COPY OF PAPERS
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TRANSMITTAL LETTER

Sir:

Enclosed herewith are three copies of the Appeal Brief in the above-identified application.

Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of \$320 for payment of the appeal fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

10/2002 MPEOPLES 00000001 193880
FC:117 920-00 CH Enclosed is a Petition for Extension of Time.

Respectfully submitted,

Ronald S. Hermenau
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Attorney for Applicants
Reg. No. 34,620

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Princeton, NJ 08543-4000
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Date: March 14, 2002



CASE LA 24A

CERTIFICATE OF MAILING

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March 14, 2002
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF

Art Unit: 1614

ROBL ET AL.

Examiner: Bahar, Mojdeh.

APPLICATION NO: 09/391,053

FILED: September 7, 1999

FOR: METHOD FOR TREATING DIABETES EMPLOYING AN AP2
INHIBITOR AND COMBINATION

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an Appeal from the Examiner's Final Rejection dated September 7, 2001, rejecting claims 1-11, and 14-15. Appellants filed a Notice of Appeal pursuant to 37 C.F.R. §1.91 on January 14, 2002. Please charge the fee due for filing this brief (\$320.00) to Deposit Account No. 19-3880. In the event that the actual fee differs from that specified, it is requested that the overpayment or underpayment be credited or charged to the stated account number. Two copies of this Appeal Brief accompany the submission.

(1) REAL PARTY IN INTEREST

The real party in interest in this appeal is Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000. Bristol-Myers Squibb Company is the assignee and owner of the entire interest in the above-identified application by virtue of an assignment which was recorded in the United States Patent and Trademark Office on September 7, 1999 at Reel/Frame 010229/0946.

RELATED APPEALS AND INTERFERENCES

The undersigned knows of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) STATUS OF CLAIMS

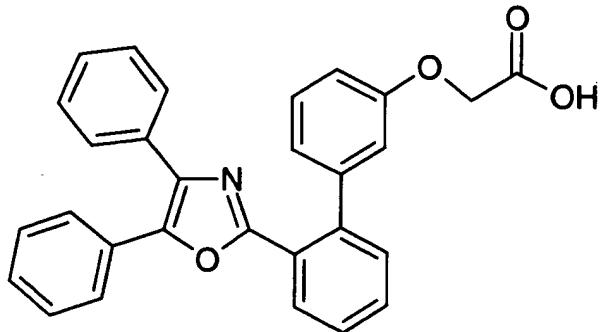
Claims 1, 2, 5-11, 14 and 15 are pending.

Claims 3, 4, 12, 13 and 16-20 have been cancelled.

No claims have been allowed.

Claims 1, 2, 5-11, 14 and 15 stand rejected under 35 U.S.C. §103 as being unpatentable over Hotamisligil in view of Failli

As a result of restriction practice, claims 1, 2, 5-11, 14 and 15 have been examined to extent they read on a method of treating diabetes with the following ultimate species of aP2 inhibitor:



(4) STATUS OF AMENDMENTS

In response to the Final Rejection, Appellants submitted an amendment canceling claims 3, 4, 12, 13 and 16-20. The Examiner entered this amendment.

Appellants note that the current form of claim 5 is inappropriate, as being dependent upon a cancelled claim (claim 3). Appellants apologize for the oversight and suggest that claim 5 be amended to read as follows:

5. The method as defined in Claim 1 where said aP2 inhibitor contains a substituent which binds within and/or interacts with a discrete pocket within the aP2 protein defined by the amino acid residues designated Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2 (SEQ ID NO: 1).

A marked-up version of the proposed amendment, highlighting the additions/deletions follows:

5. The method as defined in Claim 31 where said aP2 inhibitor contains ~~an additional~~ a substituent which binds within and/or interacts with a discrete pocket within the aP2 protein defined by the amino acid residues designated Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2 (SEQ ID NO: 1).

(5) SUMMARY OF INVENTION

The invention relates to a method of treating, *inter alia*, diabetes comprising the administration of an effective amount of an aP2 inhibitor (see specification at page 1, lines 5-11). While the invention encompasses the use of aP2 inhibitors to treat other disorders (such as hyperglycemia, hyperinsulinemia, obesity, etc), the claims have only been examined to the extent they read on the use of the Appellants' selected species of aP2 inhibitor to treat diabetes.

aP2 is an abundant cytosolic protein in adipocytes that is involved in the regulation of fatty acid trafficking in adipocytes, and mediates fatty acid fluxes in adipose tissue (see specification at page 1, lines 22-26). aP2 is believed to be central to the pathway that links obesity to insulin resistance (see specification at page 1, lines 26-36). The aP2 inhibitors suitable for use in the invention are compounds which bind to the aP2 protein and inhibit its function and/or its ability to bind free fatty acids (see specification at page 2, lines 33-36). Preferred aP2 inhibitors include compounds containing a hydrophobic substituent that binds to (in) and/or interacts with a discrete pocket within the aP2 protein defined by the amino acid residues designated Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2 (SEQ ID NO: 1) (see specification at page 3, lines 12-27). This pocket is illustrated in the x-ray data presented in Appellant's Figure 1 (see specification at page 33, line 22 to page 34, line 28).

Appellants are unaware of any prior art directed to the use of aP2 inhibitors to treat diabetes. Appellants have discovered that numerous known compounds are capable of inhibiting aP2 (see specification at pages 4-22). While these compounds—themselves—were known in the art (Appellants are making no attempt to obtain claims covering these specific compounds as composition-of-matter), their ability to inhibit aP2 was not appreciated and thus their potential to treat diabetes is not suggested. Appellants are thus the first to identify a plurality of aP2 inhibitors (identifying them as such) and disclose their use to treat diabetes.

(6) ISSUES

Whether the Examiner has improperly characterized Appellants' description of their own discovery (appearing in the specification language at page 4, lines 2-7) as an admission of the content of the prior art Failli reference.

(7) GROUPING OF CLAIMS

For purposes of the issue presented in this appeal, the claims stand or fall together. This grouping is applicable to the specific rejection of record. Appellants reserve the right to modify the grouping of claims if new grounds of rejection are entered.

(8) ARGUMENT

The Rejection On Appeal

The Examiner has rejected claims 1, 2, 5-11, 14 and 15 under 35 U.S.C. §103 as being unpatentable over Hotamisligil in view of Failli (U.S. 5,218,124). As correctly noted by the Examiner, Hotamisligil does not disclose any aP2 inhibitor, or even the use of aP2 inhibition to treat diabetes (instead this reference discloses that genetically modified aP2-deficient mice on a high fat diet did not tend to develop insulin resistance or diabetes similar to control mice). In order to support a proper §103 rejection, the Examiner attempts to fill-in Hotamisligil's missing gap with the Failli reference (disclosing the elected ultimate species of aP2 inhibitor). However, rather than rely on the actual content of the Failli disclosure, the Examiner's rejection is based solely on a purported "admission" made in the specification concerning the scope of the Failli disclosure.

A simple review of the cited Failli reference reveals that the authors did not appreciate the fact that the disclosed compounds were capable of inhibiting aP2. Instead, Failli et al. only recognized their compounds to be useful as inhibitors of a different target-- PLA₂. As inhibitors of PLA₂ Failli recognized that the disclosed compounds would be useful in treating disorders such as allergic rhinitis, allergic bronchial asthma, and gastric cytoprotective agents. Failli does not disclose or suggest that these compounds could be useful to treat diabetes or any of the other disorders covered by Appellants' application. When Appellants pointed this fact out to the Examiner (see Response dated June 21, 2001 at page 3), the Examiner clarified that the rejection was not based on the actual disclosure of Failli, but rather on a purported "admission" made in Appellants specification:

"Applicant's remarks that Failli et al. (USPN 5,218,124) teaches that compounds at issue (i.e., oxazole derivatives) are PLA2 inhibitors and not aP2 inhibitors have been considered but are not found persuasive to overcome the rejection. Note that in the first office action, the examiner has referred to Failli et al. (USPN 5,218,124) as disclosed in the specification beginning at the top of page 4. The examiner has cited to nothing more than the applicant's admissions regarding the prior art."

(Office Action dated September 7, 2001 at pp 4-5) (emphasis in original).

As explained further below, the Examiner has manufactured this "admission regarding prior art" from Appellants description of their own invention.

The Manufactured "Admission"

The specification language from which the Examiner manufactures this dubious admission is reproduced below:

Detailed Description of the Invention

Examples of aP2 inhibitors suitable for use herein include compounds which include an oxazole or analogous ring. Thus, U.S. Patent No. 5,218,124 to Failli et al (the disclosure of which is incorporated herein by reference) discloses compounds, which have activity as aP2 inhibitors and thus suitable for use herein.....

(Specification page 4 lines 1-7).

This statement appears directly under the banner "Detailed Description of the Invention" wherein the Appellants have described **their own invention**. The language latched-onto by the Examiner, merely observes the fact that Appellants have discovered that Failli's known compounds have an additional—unrecognized—utility. This discovery of a new use for Failli's compounds, and a new method of treating diabetes is patentable. It is improper for the Examiner to use Applicants' own disclosure/description of the invention as prior art to reject the claims on appeal. See, In re Pleuddemann, 15 USPQ2d 1738, 1742 (Fed. Cir. 1990).

Conclusion

The "admission" relied-upon by the Examiner is improperly derived from Appellants' description of the their own patentable invention. Such statements do not constitute prior art. The Examiner's rejection is built upon a faulty foundational premise and should be reversed. The cited art neither discloses the inhibition of aP2 to treat diabetes nor the use of the elected species to treat diabetes, and thus the claims on appeal should be allowed to issue.

Respectfully submitted,

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Ronald S. Hermenau
Ronald S. Hermenau
Attorney for Applicants
Reg. No. 34,620

Date: 3/14/01

CLAIMS ON APPEAL

1. A method for treating diabetes, insulin resistance, obesity, hyperglycemia, hyperinsulinemia, or elevated fatty acids, glycerol, or atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 inhibitor.

2. The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids.

5. The method as defined in Claim 3 wherein said aP2 inhibitor contains an additional substituent which binds within and/or interacts with a discrete pocket within the aP2 protein defined by the amino acid residues designated Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2.

6. The method as defined in Claim 5 wherein said additional substituent in said aP2 inhibitor is hydrophobic in nature.

7. The method as defined in Claim 5 in which the through space distance from the hydrogen bond donor/acceptor group and the additional substituent group in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.

8. The method as defined in Claim 1 wherein Type II diabetes is treated.

9. The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

10. The method as defined in Claim 1 wherein the aP2 inhibitor includes an oxazole or analogous ring, a pyrimidine derivative or a pyridazinone derivative.

11. The method as defined in Claim 10 wherein the aP2 inhibitor is a substituted benzoyl or biphenyl-2-oxazole-alkanoic acid derivative, an oxazole derivative, a 2-thio-4,5-diphenyloxazole S-derivative, a phenyl-heterocyclic oxazole derivative, a diaryloxazole derivative, a 4,5-diphenyloxazole

derivative, an oxazole carboxylic acid derivative, a phenyloxazolyloxazole derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acid derivative.

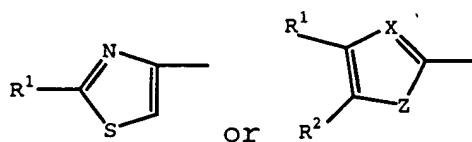
14. The method as defined in Claim 10 wherein the aP2 inhibitor is

(I) a substituted benzoylbenzene or biphenyl alkanoic acid derivative having the structure:

I $A(CH_2)_nO-B$

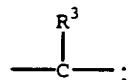
wherein

A is a group having the formula

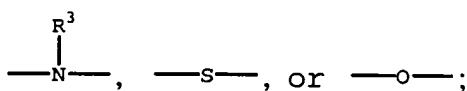
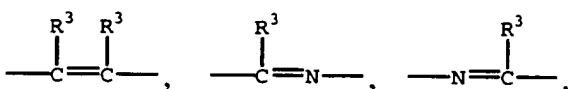


wherein

X is -N- or



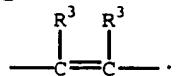
Z is



R¹ is hydrogen, lower alkyl or phenyl;

R² is hydrogen or lower alkyl; or

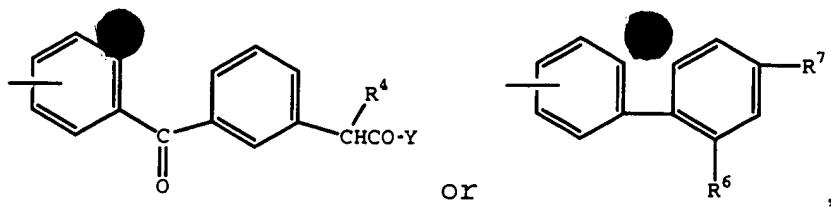
R¹ and R² taken together form a benzene ring, with the proviso that when X is -N-, Z is other than



R³ is hydrogen or lower alkyl;

n is 1-2;

B is



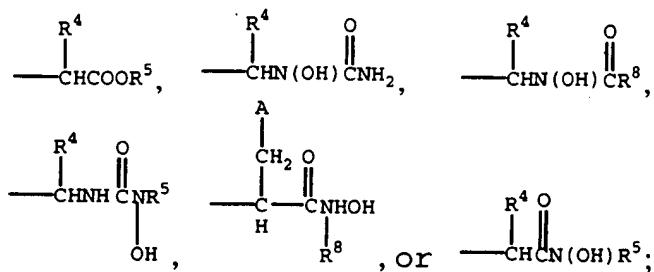
wherein

Y is OR⁵ or N(OH)R⁸;

R⁴ and R⁵ are each, independently, hydrogen or lower alkyl;

R⁶ is hydrogen, halo or nitro;

R⁷ is



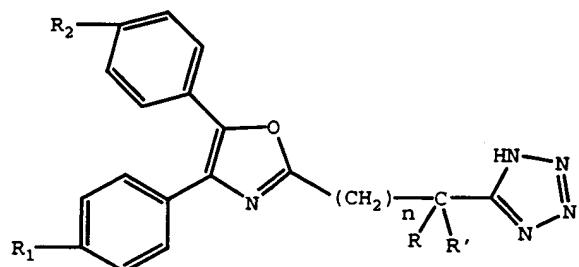
R⁸ is lower alkyl;

m is 0-3;

or a pharmacologically acceptable salts thereof;

(II) oxazole derivatives which have the structure

II



in which;

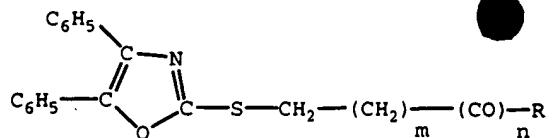
R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

R₁ and R₂ are identical or different and represent hydrogen or halogen atoms or alkyloxy radicals in which the alkyl portion contains 1 to 4 carbon atoms in a straight or branched chain, and

n equals 3 to 6, as well to their salts;

(III) 2-thiol-4,5-diphenyloxazole S-derivatives which have the structure

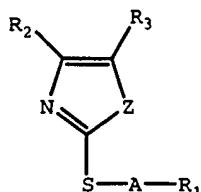
III



wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino, and pharmaceutically acceptable addition salts thereof;

(IV) azole derivatives of the structure

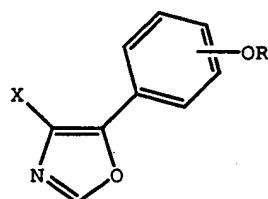
IV



wherein R₁ is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R₂ and R₃ each are aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an integer from 1 to 10, inclusive; and Z is O or S, and physiologically acceptable salts thereof;

(V) phenyl-heterocyclic oxazole derivatives which have the structure

V

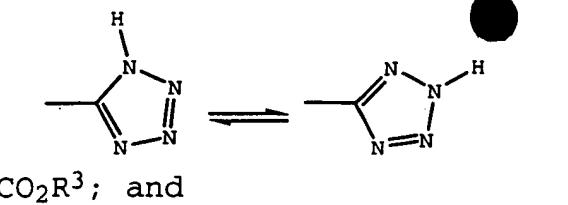


X is

R is CH_2R^2 ;

R¹ is Ph or Th;

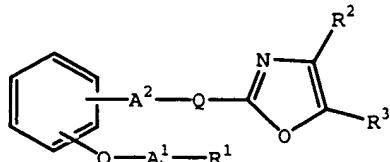
R^2 is



R^3 is H, or $\text{C}_1\text{-C}_4$ lower alkyl;

or pharmaceutically acceptable salt thereof;

(VI) diaryloxazole derivatives having the structure VI



wherein R^1 is carboxy or protected carboxy,

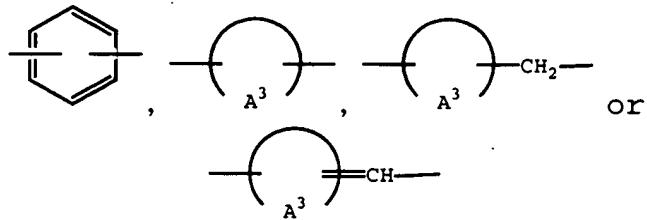
R^2 is aryl,

R^3 is aryl,

A^1 is lower alkylene,

A^2 is bond or lower alkylene and

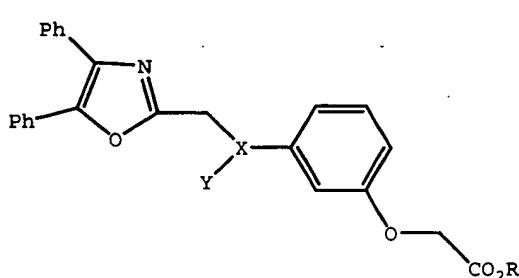
$-\text{Q}-$ is



(in which A^3 is cyclo (lower)alkane or cycle(lower)alkene,

each of which may have suitable substituent(s));

(VII) 4,5-diphenyloxazole derivatives having the structure VIIA



wherein

R is H or $\text{C}_1\text{-C}_5$ lower alkyl,

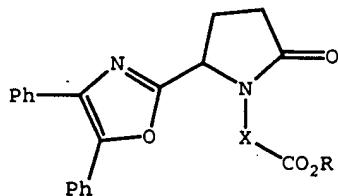
X is N or CH,

Y is H or $\text{C}_1\text{-}\text{C}_5\text{R}^1$, or COR^2 , provided that when X is CH, Y is not H,

R^1 is $\text{C}_1\text{-}\text{C}_5$ lower alkyl, or phenylmethyl, and

R^2 is $\text{C}_1\text{-}\text{C}_5$ alkyl;

VIIIB



wherein

R is H or $\text{C}_1\text{-}\text{C}_5$ lower alkyl,

X is $(\text{CH}_2)_n$ or para or meta substituted phenyl wherein the substituent is OR^2 ,

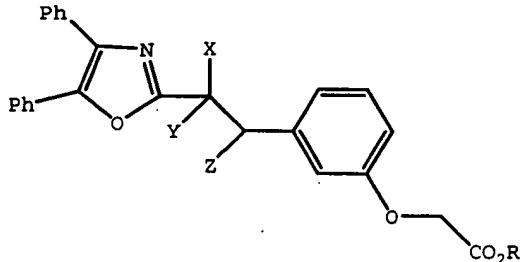
R^2 is $\text{C}_1\text{-}\text{C}_5$ alkyl, and

n is an integer of 4 to 8,

and pharmaceutically acceptable salts thereof;

(VIII) oxazole carboxylic acid derivatives having the structure

VIII



wherein

Y and Z are independently hydrogen or together form a bond;

X is CN, CO_2R^1 or CONR^2R^3 ;

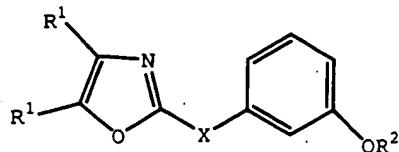
R and R^1 are independently or together H, Na, or $\text{C}_1\text{-}\text{C}_5$ lower alkyl;

R^2 and R^3 are independently or together H, or $\text{C}_1\text{-}\text{C}_5$ lower alkyl;

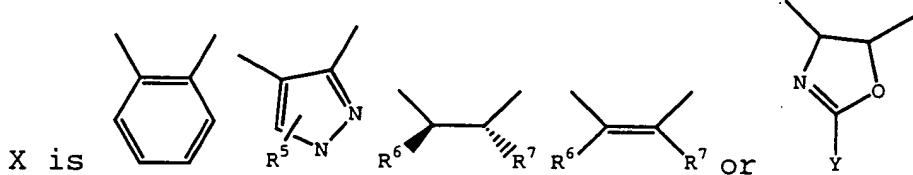
or alkali metal salt thereof;

(IX) phenyloxazolyloxazole derivatives having the structure

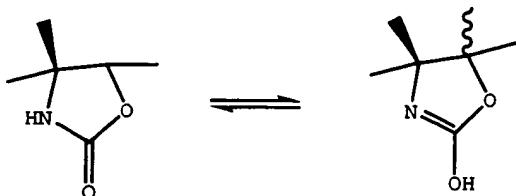
IX



wherein



Y is CH₃, Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautomerism form



R¹ is Ph or Th;

R² is CH₂R³;

R³ is CO₂R⁴;

R⁴ is H or C₁-C₅ lower alkyl;

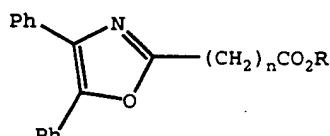
R⁵ is H or CH₃; R⁶ is OHCHN or H₂N; and

R⁷ is H or OH;

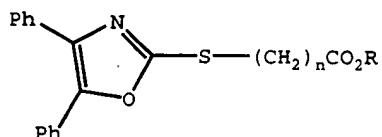
or pharmaceutically acceptable salt thereof;

(X) 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acids and esters having the structure

XA

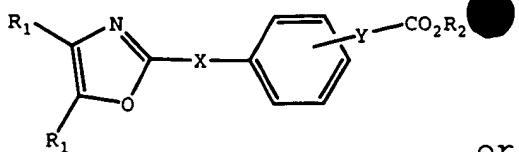


XB



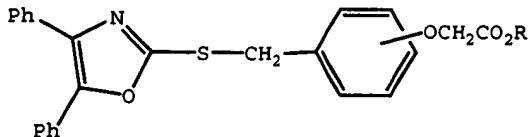
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



or

XD



wherein

R_1 is phenyl or thiienyl;

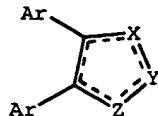
R_2 is hydrogen, lower alkyl or together with CO_2 is tetrazol-1-yl;

X is a divalent connecting group selected from the group consisting of CH_2CH_2 , $CH=CH$, and CH_2O ;

Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of OCH_2 , CH_2CH_2 and $CH=CH$,

or when R_2 is hydrogen, an alkali metal salt thereof;

(XI) substituted 4,5-diaryl heterocycles having the formula XI



in which

each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR^1 ;

Y is nitrogen, $N(CH_2)_nA$ or $C(CH_2)_nA$;

Z is nitrogen, oxygen or $N(CH_2)_nA$, and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

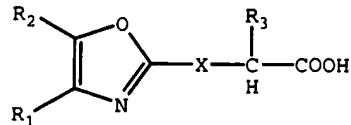
R^1 is hydrogen, C_{1-4} alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

n is 4 to 12; and

A is CO_2H or a group hydrolysable to CO_2H , 5-tetrazolyl, SO_3H , $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4} alkyl, or a pharmaceutically acceptable salt thereof;

(XII) compounds which have the structure

XII



Where x is 0 or s;

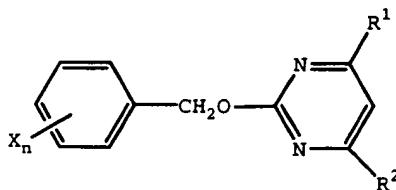
R_1 is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

R_2 is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

R₃ is H or alkyl;

(XIII) 2-benzyloxypyrimidine derivatives having the following structure

XIII



wherein

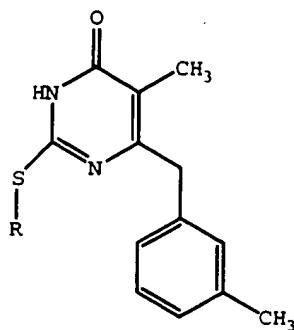
R^1 and R^2 are each independently H, a halogen, hydroxyl, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₅ alkenyl, C₃-C₅ alkynyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₃-C₅ alkenyloxy, C₃-C₅ alkynyloxy, C₁-C₄ alkylthio, or phenyl, with the proviso that at least one of R^1 and R^2 must be hydroxyl;

n is an integer of 0 to 5; and

each X which may be identical or different if n is greater than 1, is a halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₇-C₉ aralkyloxy, phenyl, hydroxymethyl, hydroxycarbonyl, C₁-C₄ alkoxy carbonyl, or nitro;

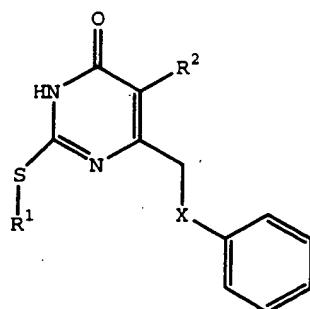
(XIV) dihydro(alkylthio)-(naphthylmethyl)-oxopyrimidines which have the structures

XIVA



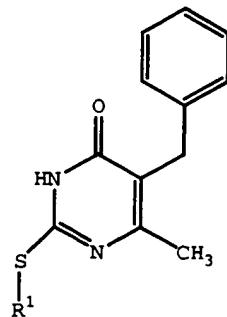
3a R=sec-butyl
 3b R=cyclopentyl
 3c R=cyclohexyl

XIVB

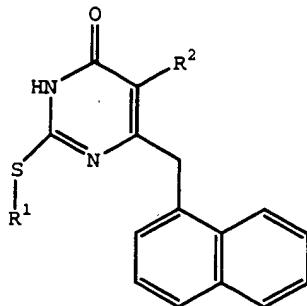


5 X=CH₂
 6 X=O
 7 X=S

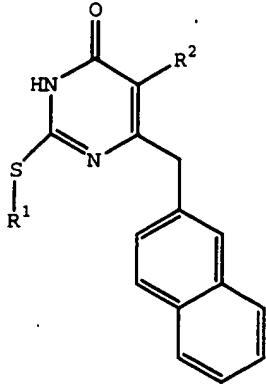
XIVC



XIVD



XIVE

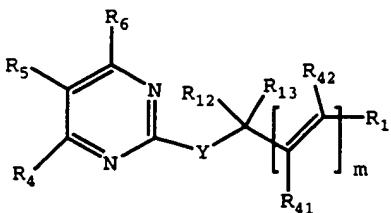


R^1 = sec-butyl, cyclopentyl, cyclohexyl;

R^2 = H, CH_3 , including tautomers of the above;

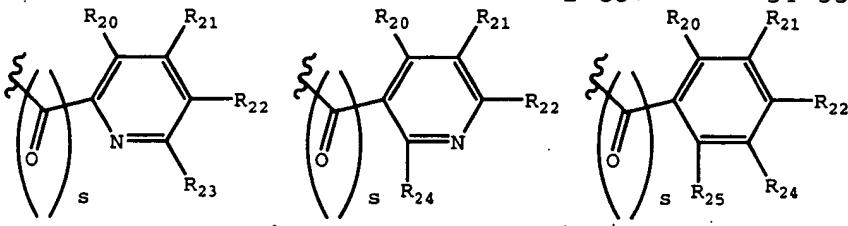
(XVI) α -substituted pyrimidine-thioalkyl and alkylether compounds which have the structure

XVI



where m is 0 or 1;

R^1 is selected from $-CO_2R_{53}$, $-CONR_{54}R_{55}$,



where s is 0 or 1, and R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , and R_{25} are the same or different and are selected from $-H$, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_8 cycloalkyl, $-CF_3$, $-NO_2$, $-halo$, $-OH$, $-CN$, phenyl, phenylthio, styryl, $-CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C(OH)(R_{31}(R_{33})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $(CH_2)_nN(R_{31})(SO_2(R_{33}))$, or where R_{20} and R_{21} , or R_{21} and R_{22} , or R_{22} and R_{23} are taken together to form a five or six-membered saturated or unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-OH$, $-CH_2OH$, $-(CH_2)_n-N(R_{31})(R_{32})$, C_3-C_8 cycloalkyl, $-CF_3$, $-halo$, $CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $-(CH_2)_nN(R_{31})(SO_2(R_{33}))$, $-CN$, $-CH_2CF_3$ or $-CH(CF_3)_2$, or phenyl and the saturated ring may be optionally

substituted with 1, 2 or 3, -C₁-C₆ alkyl, -C₁-C₆ alkoxy, -OH, -CH₂OH or -(CH₂)_n-N(R₃₁)(R₃₂) or one oxo (=O);

where n is 0-3 and R₃₁, R₃₂ and R₃₃ are the same or different and are selected from

-H,

C₁-C₆ alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH or -CN,

or where R₃₁ and R₃₂ taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C₁-C₆alkyl)piperazinyl, or a member selected from

1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methylinden-2-yl, 3,4-dihydronaphth-1-yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;

where R₅₃ is selected from -H, C₁-C₆alkyl, C₃-C₆cycloalkyl, phenyl (optionally substituted with 1, 2, or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH, -CN), or a five or six-membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with -H, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂);

where R₅₄ and R₅₅ being the same or different are selected from -H, C₁-C₆ alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy or -CF₃), or taken together with the attached nitrogen to form a ring selected from -

pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C₁-C₆alkyl)piperazinyl;

R₄₁ and R₄₂, being the same or different, are selected from -H and C₁-C₄ alkyl;

R₁₂ is selected from -H, C₁-C₆ alkyl, -C₃-C₆ cycloalkyl, -CN, -C(O)NH₂, -C(O)N(C₁-C₆alkyl)(C₁-C₆alkyl), -CO₂H, -CO₂(C₁-C₆alkyl), -CH₂OH, -CH₂NH₂ or -CF₃;

R₁₃ is selected from -H, C₁-C₆ alkyl or -CF₃;

Y is selected from -S-, -S(O)-, -S(O)₂, or -O_r;

R₄ is -OH;

R₅ is selected -H, -C₂H₄OH, -C₂H₄-O-TBDMS, halo, -C₃-C₆ cycloalkyl, C₁-C₃ alkoxy, -CH₂CH₂Cl or C₁-C₄ alkyl, with the proviso that R₅ is not isobutyl;

or, when R₆ is hydroxyl, R₄ and R₅ are taken together to form a five or six-membered saturated or unsaturated ring which together with the pyrimidine ring form the group consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine, pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆ alkyl C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂), -C₃-C₈ cycloalkyl, -CF₃, -halo, -CO₂(R₃₁), -CON(R₃₁)(R₃₂), -CO(R₃₁), -(CH₂)_nN(R₃₁)(CO(R₃₃)), -(CH₂)_nN(R₃₁)(SO₂(R₃₃)), and the saturated ring may be optionally substituted with 1, 2 or 3, -C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, -CH₂OH, or -(CH₂)_n-N(R₃₁)(R₃₂) or one oxo (=O); and

R₆ is selected from -H, -OH, halo, -CN, -CF₃, -CO₂(R₆₁), -C(O)R₆₁ or -C(O)N(R₆₁)(R₆₂) where R₆₁ and R₆₂ are the same or different and are selected from

-H,

C₁-C₆ alkyl,

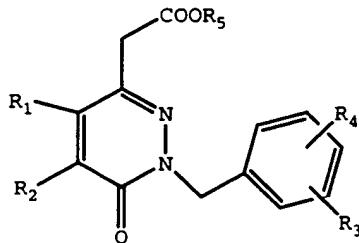
phenyl optionally substituted with 1, 2 or 3 -halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, -OH, -CN,

or where R₆₁ and R₆₂ taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl,

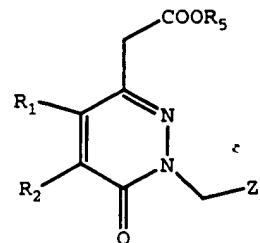
-4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C₁-C₆ alkyl)piperazinyl;

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof;

(XVII) compounds which have the structure



XVIIA



XVIIIB

where R₁ and R₂ are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF₃, CH₃O, CH₃S, NO₂, or R₁ and R₂ with the carbons to which they are attached can form methylenedioxy, or

R₁ and R₂ can form a C₃-C₇ non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen containing heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted with halogen or alkyl,

R₃ and R₄ are H, alkyl, halogen, CF₃, CH₃O, CH₃S or NO₂ or R₃ and R₄ with the carbons to which they are attached can form a methylenedioxy group,

R₅ is H, and

Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

15. The method as defined in Claim 1 wherein the aP2 inhibitor has the structure

